

**Errata to FDA Briefing Document  
for the September 11, 2007 joint meeting of the  
Cardiovascular and Renal Drugs Advisory Committee  
with the Drug Safety and Risk Management Advisory Committee**

The Committees will discuss updated information on the risks and benefits of erythropoiesis-stimulating agents (ARANESP, Amgen, Inc., EPOGEN, Amgen, Inc. and PROCRIT, Amgen, Inc.) when used in the treatment of anemia due to chronic renal failure.

Item 1) Page 3, paragraph 3, sentence 2:

Current:

"However, serious cardiovascular risks have been shown for patients who attain hemoglobin levels in excess of 12 g/dL in two randomized, controlled studies that compared the "targeting" of higher hemoglobin/hematocrit levels to lower levels (see "Normal hematocrit" and CHOIR studies in subsequent information."

Replaced with:

"However, serious cardiovascular risks have been shown for patients "targeted" to hemoglobin levels in excess of 13 g/dL in two randomized, controlled studies that compared the "targeting" of higher hemoglobin/hematocrit levels to lower levels (see "Normal hematocrit" and CHOIR studies in subsequent information."

Item 2) Page 6, paragraph 3 in section 2, sentence: bullet 2 under Epoetin alfa:

Current:

"-1991: approved for use among zidovudine-treated HIV-infected patients"

Replaced with:

"-1990: approved for use among zidovudine-treated HIV-infected patients"

Item 3) Page 7, paragraph 1, sentence 1:

Current:

"In the clinical studies supporting approval, ESAs were administered to achieve and maintain hematocrit values of approximately 32% to 38% (Epogen/Procrit) or hemoglobin concentrations of approximately 9 to 13 g/dL (Aranesp)."

Replaced with:

"In the clinical studies supporting approval, ESAs were administered to achieve and maintain hematocrit values of approximately 32% to 38% (Epogen/Procrit) or hemoglobin concentrations within - 1 to + 1.5 g/dL of the baseline level and within 9 to 13 g/dL (maintenance) or 11 to 13 g/dL (correction) (Aranesp)."

Item 4) Page 7, paragraph 5, sentence 1:

Current:

"Shortly following submission of the major CHOIR study findings to the FDA, new study data were also supplied that described adverse cardiovascular or mortality findings for the use of ESAs in the perisurgical setting or in the treatment of chemotherapy-induced anemia among cancer patients."

Replaced with:

"Shortly following submission of the major CHOIR study findings to the FDA, new study data were also supplied that described adverse cardiovascular or mortality findings for the use of ESAs in the perisurgical setting or among certain cancer patients."

Item 5) Page 9, paragraph 1 in section 4a, , sentence 2:

Current:

"The study, conducted between 1993 and 1996, was terminated early due to the detection of important safety considerations."

Replaced with:

""The study, with investigational therapeutic intervention conducted between 1993 and 1996 and follow-up extended through 1997, was terminated early due to the detection of important safety considerations."

Item 6) Page 10, second full paragraph, sentence bullets a and b:

Current:

"a) had a diagnosis of end stage renal disease for a minimum of three months;  
b) had been undergoing hemodialysis and receiving epoetin alfa treatment for a minimum of at least 4 weeks prior to enrollment;"

Replaced with:

"a) had a diagnosis of end stage renal disease and were undergoing hemodialysis and receiving epoetin alfa treatment for a minimum of three months;  
b) had a stable hematocrit of 30%  $\pm$  3% for a minimum of at least 4 weeks prior to enrollment."

Item 7) Page 10-11, first paragraph after Table 1, sentence 2:

Current:

"Overall, the log rank test of event free survival was 0.01, favoring the low hematocrit group. The relative risk for a primary endpoint event was 1.3 (95% CI of 0.90 to 1.72) for patients in the high hematocrit group compared to those in the low hematocrit group."

Replaced with:

"Overall, the log rank test of event free survival yielded a p value of 0.01, favoring the low hematocrit group. The unadjusted relative risk for a primary endpoint event was 1.28 (95% CI of 1.06 to 1.56) for patients in the high hematocrit group compared to those in the low hematocrit group."

Item 8) Page 13, Table 2, fourth row; Page 14, Table 3, third row; Page 25, paragraph 5, sentence 5:

Current:

"CHF hospitalization"

Replaced with:

"CHF hospitalization (without renal replacement therapy)"

Item 9) Page 17, paragraph 1, sentence 1:

Current:

"Conceivably, information from the TREAT study may importantly impact the use of ESAs since this study is designed, in part, to compare to the targeting of a higher hemoglobin level to a lower level."

Replaced with:

"Conceivably, information from the TREAT study may importantly impact the use of ESAs since this double-blind, placebo-controlled study is designed to evaluate the effect of anemia therapy with darbepoetin alfa on the composite event of all-cause mortality and nonfatal cardiovascular events in anemic nondialysis CRF patients with type 2 diabetes mellitus."

Item 10) Page 17, paragraph 4, sentence 1:

Current:

"The study uses a double-blind design and a composite primary endpoint (time to event) of all cause mortality and cardiovascular events (acute myocardial ischemia, congestive heart failure requiring medical attention, myocardial infarction or cerebrovascular accident)."

Replaced with:

"The study uses a double-blind design and a composite primary endpoint (time to event) of all cause mortality and nonfatal cardiovascular events (acute myocardial ischemia, congestive heart failure requiring medical attention, myocardial infarction or cerebrovascular accident)."

Item 11) Page 18, paragraph 1, sentence 2 and all additional citations to the draft guidance document:

Current:

"Specifically, FDA requested that these data be reassessed to determine the extent to which these data met the recommendations described in the 2006 FDA document entitled, "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims."

Replaced with:

"Specifically, FDA requested that these data be reassessed to determine the extent to which these data met the recommendations described in the 2006 draft FDA document entitled, "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims."

Item 12) Page 20, paragraph 6, sentence 2:

Add the sentence:

"Additionally, a review of all published Epogen studies with PRO endpoints was provided."

Item 13) Page 20, paragraph 8, third bullet under Study 8601:

Current:

"-no description of missing data or extent of compliance with PRO assessments"

Replaced with:

"-no description of missing data"

Item 14) page 21, Table 4 and all portions of document that refer to "study 8604":

Current:

"8604"

Replaced with:

"EP86-004"

Item 15) Page 23, paragraph 2, third sentence, third bullet:

Current:

"-inconsistent results between the six minute walk and treadmill test"

Replaced with:

"-inconsistent results between the six minute walk and exercise stress test (at six months, the combined epoetin alfa groups exercised for significantly longer than placebo in the exercise stress test, however a statistically significant difference was not shown between the combined epoetin alfa groups and placebo at six months in the six minute walk test)"

Item 16) Page 23, paragraph 3, second bullet under all study summaries:

"-all studies were not powered to detect changes in PRO/"quality of life"

Replaced with:

"-the clinical protocol description of study design features generally did not describe the powering of the studies to detect changes in PRO/"quality of life"

Item 17) Page 25, paragraph 5, sentence 4:

Current:

"The study was hoped to demonstrate improved outcomes in subjects randomized to the higher hematocrit."

Replaced with:

"The study was hoped to demonstrate improved outcomes in subjects randomized to the higher hemoglobin."

Item 18) Page 25 footnote to correct spelling:

Current:

"Sinhg AK. Szczech E. Kang UL, et al."

Replaced with:

"Singh, AK. SZczech, E., Tang, UL, et al.."

Item 19) Page 26, first paragraph after the boxed warning, sentence 1:

Current:

"The principle underlying the NHCT and CHOIR Studies was that the optimum hematocrit for a patient with chronic renal failure should be largely no different from than that of healthy individuals."

Replaced with:

"One interpretation of the principle underlying the NHCT and CHOIR Studies was that the optimum hematocrit for a patient with chronic renal failure should be largely no different from that of healthy individuals."

Item 20) Page 26, first paragraph after the boxed warning, sentence 5 and page 30, paragraph 1, sentence 2:

Current:

"These were larger studies that examined a broad spectrum of patients with chronic renal failure: NHCT (n = 1233) included patients with a history of ischemic heart disease or congestive heart failure who were on hemodialysis;"

Replaced with:

"These were larger studies that examined a broad spectrum of patients with chronic renal failure: NHCT (n = 1233) included patients with clinically evident ischemic heart disease or congestive heart failure who were on hemodialysis and receiving Epoetin alfa;"

Item 21) Page 28, paragraph 1, sentence 6:

Current:

"The subject presented in the top panel (#1001) was randomized to the "normal" hemoglobin target (11 - 13 g/dL); the subject presented in the lower panel (#1002) was randomized to the lower target (9 - 11 g/dL)."

Replaced with:

"The subject presented in the top panel (#1001) was randomized to the "normal" hemoglobin target; the subject presented in the lower panel (#1002) was randomized to the lower target."

Item 22) Page 49, paragraph 1, sentence 1 and Page 50, second paragraph under Figure 13, sentence 2:

"The sponsors cite summaries of analyses by Kilpatrick (2007) and Singh (2006) that show..."

Replaced with:

""The sponsors cite summaries of analyses by Kilpatrick (2007) and Johnson & Johnson PRD that show..."

Item 23) Page 52, paragraph 5, sentence 2:

Current:

"Studies should be conducted to determine whether ESA-unresponsive patients can be identified, and, if so, how to best manage their risk."

Replaced with:

"Studies should be conducted to determine whether ESA-unresponsive/hypo-responsive patients can be identified, and, if so, how to best manage their risk."